REMARKS

This is meant to be a complete response to the Office Action mailed June 30, 2004. In the Office Action, the Examiner rejected Applicants' claims 1-9, 12-17 and 31 under 35 U.S.C. 102(b) as being anticipated by Celia et al. The Examiner also rejected Applicants' claims 1-9, 12-17 and 31 under 35 U.S.C. 103(a) as being unpatentable over Celia et al. in view of Albani. In addition, the Examiner rejected Applicants' claims 10-11 under 35 U.S.C. 103(a) as being unpatentable over Celia et al. in view of Albani and further in view of Plant et al. and Walter et al.

Applicants' Response to the 35 U.S.C. 102(b) Rejection

In the Office Action, the Examiner rejected Applicants' claims 1-9, 12-17 and 31 under 35 U.S.C. 102(b) as being anticipated by Celia et al. Applicants respectfully traverse the rejection based on the amendments to the claims and for the reasons stated herein below.

Amended claim 1, and therefore claims 2-9 and 12-17 which depend therefrom, recite a complex that includes a liposome and at least one recombinant soluble MHC-peptide complex that is incorporated into the liposome such that the at least one recombinant soluble MHC-peptide complex is available to bind to a T cell receptor on a T cell, thereby activating or suppressing the T cell. The recombinant soluble MHC-peptide complex includes

(1) a recombinant soluble MHC heavy chain molecule containing a tag for anchoring the recombinant soluble MHC-peptide complex to the liposome; (2) a beta-2-microglobulin molecule **native to and endogenously expressed in a host cell** having a construct encoding the recombinant soluble MHC heavy chain molecule, wherein the beta-2-microglobulin is associated with the recombinant soluble MHC heavy chain molecule in the host cell; and (3) an **endogenously produced peptide** bound to an antigen binding groove of the recombinant soluble MHC heavy chain molecule, wherein the endogenously produced peptide is ***loaded*** **into the antigen binding groove of the recombinant soluble MHC heavy chain molecule *in the host cell*.**

Amended claim 31 recites an artificial antigen presenting cell including a spherical molecule having a bilayer and at least one recombinant soluble MHC-peptide complex as described herein above, wherein the at least one recombinant soluble MHC-peptide complex is attached to the spherical molecule via interactions between the tag and the bilayer such that the at least one recombinant soluble MHC-peptide complex is available to bind a T cell receptor on a T cell, thereby activating or suppressing the T cell.

Celia et al. teach a soluble His-tagged H-2K^b MHC Class I molecule captured and oriented on a lipid membrane. The purification of the soluble form of H-2K^b was performed as described in Matsumura et al. (1992) (submitted herewith in a Supplemental IDS), which teaches expression of H-2K^b

in transfected *Drosophila melanogaster* cells. A person having ordinary skill in the art would recognize that *Drosophila melanogaster* cells do not have the necessary machinery for peptide processing and loading, and therefore the molecules purified by the methods of Matsumura et al. are heterodimers of heavy chain and beta-2-microglobulin which are **empty** and therefore **devoid of endogenous peptides** (see Abstract and Page 23589, Column 2, paragraph 4 - Page 23590, Column 1, paragraph 1). Indeed, Celia et al. teach that the peptide-binding groove of the H-2K^b molecules was available for binding to an antibody and was exposed to solvent after captured on the lipid membrane, and thus did not have a peptide loaded therein. For binding experiments with soluble T cell receptors, the purified H-2K^b molecule were loaded *in vitro* with a high affinity peptide (see Page 5636, Column 2, paragraph 2).

In addition, the beta-2-microglobulin of the heterodimer taught by Matsumura et al. (and therefore also taught by Celia et al.) is a **recombinantly produced** molecule and thus is **not native to nor endogenously expressed in the host cell** (see Page 23590, Column 1, paragraph 1 of Matsumura et al., 1992).

Therefore, Celia et al. do not teach, disclose or even suggest a complex or artificial antigen presenting cell as taught by claims 1-9, 12-17 and 31 of the subject application, wherein the complex or artificial antigen presenting cell includes at least one recombinant soluble MHC-peptide complex comprising a

beta-2-microglobulin molecule **native to and endogenously expressed in a host cell**, and an **endogenously produced peptide *loaded* into the antigen binding groove of the recombinant soluble MHC heavy chain molecule *in the host cell***.

Thus, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(b) rejection of claims 1-9, 12-17 and 31 of the subject application as being anticipated by Celia et al.

Applicants' Response to the 35 U.S.C. 103(a) Rejection of Claims 1-9, 12-17 and 31

In the Office Action, the Examiner rejected Applicants' claims 1-9, 12-17 and 31 under 35 U.S.C. 103(a) as being unpatentable over Celia et al. in view of Albani. Applicants respectfully traverse the rejection for the reasons stated herein above in response to the 35 U.S.C. 102(b) rejection of the claims over Celia et al., and for the reasons stated herein below.

The limitations of claims 1-9, 12-17 and 31 have been described in detail herein above.

As stated hereinabove, Celia et al. do not teach, disclose or even suggest a complex or artificial antigen presenting cell that includes at least one recombinant soluble MHC-peptide complex comprising (1) a recombinant soluble MHC heavy chain molecule containing a tag for anchoring the

recombinant soluble MHC-peptide complex to the liposome; (2) *a beta-2-microglobulin molecule native to and endogenously expressed in a host cell* having a construct encoding the recombinant soluble MHC heavy chain molecule, wherein the beta-2-microglobulin is associated with the recombinant soluble MHC heavy chain molecule in the host cell; and (3) *an endogenously produced peptide loaded into the antigen binding groove* of the recombinant soluble MHC heavy chain molecule *in the host cell*.

While it is agreed that Albani teaches liposomes containing MHC:peptide complexes as well as accessory molecules and co-stimulatory molecules, the MHC molecules taught by Albani are endogenously expressed and affinity purified MHC molecules that are full length MHC molecules. In addition, the peptides utilized in the MHC:peptide complexes of Albani were bound to the MHC molecules *in vitro* **after** the MHC molecules were purified and inserted into the liposomes.

Thus, Albani adds nothing to the fact that Celia et al. do not teach, disclose or even suggest a complex or artificial antigen presenting cell that includes at least one recombinant soluble MHC-peptide complex comprising (1) a recombinant soluble MHC heavy chain molecule containing a tag for anchoring the recombinant soluble MHC-peptide complex to the liposome; (2) *a beta-2-microglobulin molecule native to and endogenously expressed in a host cell* having a construct encoding the recombinant soluble MHC heavy chain

molecule, wherein the beta-2-microglobulin is associated with the recombinant soluble MHC heavy chain molecule in the host cell; and (3) *an endogenously produced peptide loaded into the antigen binding groove of the recombinant soluble MHC heavy chain molecule in the host cell.*

Therefore, Applicants respectfully submit that claims 1-9, 12-17 and 31 are non-obvious over the combination of Celia et al. and Albani. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection of claims 1-9, 12-17 and 31 over such combination of references.

Applicants' Response to the 35 U.S.C. 103(a) Rejection of Claims 10-11

In the Office Action, the Examiner rejected Applicants' claims 10-11 as being obvious over Celia et al. in view of Albani and further in view of Plant et al. and Walter et al.

Applicants respectfully traverse the rejection based on the reasons stated herein above in response to the 35 U.S.C. 102(b) and 103(a) rejections of claims 1, 4 and 7, from which claims 10 and 11 depend, over Celia et al. or the combination of Celia et al. and Albani, and for the reasons stated herein below.

As stated herein above, the combination of Celia et al. and Albani does not teach, disclose or even suggest a complex or artificial antigen presenting cell that includes at least one recombinant soluble MHC-peptide complex comprising (1) a recombinant soluble MHC heavy chain molecule containing a

tag for anchoring the recombinant soluble MHC-peptide complex to the liposome; (2) *a beta-2-microglobulin molecule native to and endogenously expressed in a host cell* having a construct encoding the recombinant soluble MHC heavy chain molecule, wherein the beta-2-microglobulin is associated with the recombinant soluble MHC heavy chain molecule in the host cell; and (3) *an endogenously produced peptide loaded into the antigen binding groove of the recombinant soluble MHC heavy chain molecule in the host cell.*

Claims 10 and 11 include all of the limitations of claims 1, 4 and 7 from which they depend, as described herein above, as well as the further limitation that the tag attached to the recombinant soluble MHC heavy chain molecule for anchoring the recombinant soluble MHC-peptide complex to the liposome is a biotinylation signal.

Plant et al. teach derivatized liposomes with antibodies by using avidin to crosslink biotinylated phospholipid molecules in the lipid membranes with biotinylated antibody molecules. The Examiner has recognized that Plant et al. do not teach the biotinylation of soluble MHC molecules, and therefore the teachings of Plant et al. do nothing to supply the deficiencies of the teachings of Celia et al. and Albani.

Walter et al. teach soluble multimeric MHC-peptide complexes using a **mutant** beta-2-microglobulin having a biotin added thereto. In the methods of Walter et al., MHC heavy chains and the mutant beta-2-microglobulin are

recombinantly produced in *E. coli* **separately** and then are refolded **in solution** *in the presence of* ***synthetic*** *peptide*.

Walter et al. do not teach, disclose or even suggest a tag comprising a biotinylation signal peptide attached to a recombinant soluble MHC **heavy chain** molecule for anchoring the recombinant soluble MHC-peptide complex to the liposome; instead, Walter et al. teach attaching a tag to beta-2-microglobulin, wherein the beta-2-microglobulin is mutated. Walter et al. also do not teach, disclose or even suggest using a *native* beta-2-microglobulin molecule, because the multimerization step taught therein requires a *mutant* beta-2-microglobulin. Further, Walter et al. only teach *in vitro* association of the subunits. In addition, Walter et al. only teach the use of *synthetic* peptides and do not provide any teaching, suggestion or motivation for *endogenously producing* a peptide and *endogenously loading* the peptide into the antigen binding groove of the recombinant soluble MHC heavy chain molecule.

Thus, Walter et al. add nothing to the fact that the combination of Celia et al., Albani and Plant et al. does not teach, disclose or even suggest a complex or artificial antigen presenting cell that includes at least one recombinant soluble MHC-peptide complex comprising (1) a *recombinant soluble MHC heavy chain molecule containing a tag* for anchoring the recombinant soluble MHC-peptide complex to the liposome; (2) a beta-2-microglobulin molecule *native to and endogenously expressed* in a host cell

having a construct encoding the recombinant soluble MHC heavy chain molecule, wherein the beta-2-microglobulin is associated with the recombinant soluble MHC heavy chain molecule *in the host cell*; and (3) an *endogenously produced peptide* bound to an antigen binding groove of the recombinant soluble MHC heavy chain molecule and loaded into the antigen binding groove of the recombinant soluble MHC heavy chain molecule in the host cell.

Applicants respectfully submit that claims 10-11 are non-obvious over the combination of Celia et al., Albani, Plant et al. and Walter et al. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection of claims 10-11 over such combination of references.

Newly Added Claims 32-42

Claims 32-42 have been added herein. Claims 32-42 are similar to pending claims 1-16 and 31, except that claims 32-42 recite that the host cell is defective in peptide processing such that peptides are not **formed** for loading into MHC molecules, and the peptide is therefore pulsed into the host cell. However, the peptide pulsed into the cell is still *loaded endogenously* into the MHC molecule via the host cell's peptide loading machinery.

None of the prior art discussed herein above teaches, discloses or even suggests **naturally loading** a peptide into the MHC molecules of the presently claimed invention utilizing the cells' peptide loading machinery. Therefore,

Applicants respectfully submit that newly added claims 32-42 are also patentable over the art of record.

CONCLUSION

This is meant to be a complete response to the Office Action mailed June 30, 2004. Applicants respectfully submit that each and every rejection of pending claims 1-16 and 31 have been overcome. Further, Applicants respectfully submit that newly added claims 32-42 are also patentable over the art of record. Thus, Applicants respectfully submit that claims 1-6 and 31-42 are in a condition for allowance. Favorable action is respectfully solicited.

Should the Examiner have any questions regarding this Amendment, or the remarks contained herein, Applicants' agent would welcome the opportunity to discuss such matters with the Examiner.

Respectfully submitted,

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